

REMARKS

At the outset, the undersigned Applicants' representative wishes to thank Examiner Joynes for the courteous telephonic interview of August 27, 2003. The above amendments and the following remarks are believed to be consistent with the discussions with the Examiner. The above amendments should raise no new issues and are believed to put the subject application in better condition for allowance. Entry of this paper is therefore proper and is respectfully requested.

By the above amendment, Claim 1 has been revised to remove the recitation "pH-independent." Applicants are presenting the foregoing amendment for the sole purpose of advancing the prosecution of the application and without disclaimer of the removed subject matter. It is believed that the above amendment obviates the 112 rejection. As well, it is believed that the amendment clearly distinguishes the presently claimed invention from the art of record. Thus, the application is believed to be in condition for allowance and such favorable action is earnestly solicited.

In the Office Action dated May 20, 2003, Claims 1, 3-8, 10-25, and 28-30, 35, 36 and 40-42 were rejected under the second paragraph of 35 U.S.C. §112. Specifically, the Examiner objects to the recitation in Claim 1 of "pH-dependent and pH-independent delay in bisoprolol release." Claim 1 has been revised by removing the phrase "pH-independent." Accordingly, the objection is believed to be obviated and withdrawal thereof is respectfully requested.

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Turning to the art rejections. Claims 1, 3-6, 10-25, and 28-30, 35, 36 and 40-42 were rejected under 35 U.S.C. § 102(b) as being anticipated by Noda et al. (U.S. Patent No. 5,137,733). In response, Applicants respectfully submit that Noda et al. does not anticipate the presently claimed invention.

Applicants' claimed formulation comprises at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer that exhibits a pH-dependent dissolution profile and that imparts a pH-dependent delay in bisoprolol release. Noda et al. does not disclose such a formulation.

Noda et al. makes clear that its formulations are designed for dissolution that is independent of the pH. See, for example, the Abstract ("dissolution pattern irrespective of the PH of a dissolution medium"), Background of the Invention ("An object of this invention. . . and the rate of the dissolution of the medicinal compound does not depend on the pH of a medium for the dissolution"). Accordingly, the Noda et al. disclosure cannot anticipate the presently claimed invention, as it is directed to a completely different type of formulation. Applicants, therefore, respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Claims 1, 3-6, 10-25 and 28, 30, 35, 36 and 40-42 were rejected under U.S.C. § 103(a) as being unpatentable over Noda et al. In addition, those claims were rejected as being unpatentable over Noda et al. in view of the Handbook for Pharmaceutical excipients. Applicants respectfully submit that Noda et al., alone

or in combination with the Handbook for Pharmaceutical Excipients fails to render obvious the presently claimed invention.

As noted above, Applicants' claimed formulation comprises at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer that exhibits a pH-dependent dissolution profile and that imparts a pH-dependent delay in bisoprolol release. Noda et al. does not render obvious such a formulation.

Without presenting the details again, Applicants summarize that Noda et al. is directed to a pH-independent formulation, and that independence of pH is emphasized. The polymers that Noda et al. exemplifies are recognized in the art as pH-independent. And the experiments described in Noda et al. show a formulation that exhibits a pH-independent drug release profile. Clearly, pH-independence is at the very heart of the Noda et al. teaching.

The present invention, on the other hand, relies on the use of a polymer system for which the dissolution *depends* on the pH of the medium. Applicants' claimed invention is specifically formulated to exhibit a release of bisoprolol that is affected by the pH of the medium. As noted above, Applicants' claimed formulation comprises "at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer that exhibits a pH-dependent dissolution profile and that *imparts a pH-dependent delay in bisoprolol release.*" This is very clearly different from the Noda et al. formulation.

That Noda et al. fails to suggest the formulations of the subject invention is further supported by the stark differences in the correlation between *in vitro* dissolution delays and delays in *in vivo* bioavailability obtained with the Noda et al. formulations on one hand, and the correlation shown when pH-independent polymers are used in conjunction with the formulations of the invention, on the other hand. As indicated by Figures 2 and 3 of Noda et al., the Noda et al. formulations show substantially the same delay *in vitro* and *in vivo*. The Noda et al. formulations show a delay of about 8 hours prior to dissolution *in vitro* (Figure 2) and essentially no measurable plasma concentration *in vivo* until after about 8 hours from administration (Figure 3).

In contrast to the pH-independent formulations of diltiazem described in Noda et al, which shows matching *in-vitro* delays and *in-vivo* delays, the pH-independent formulation examples in the present application show that the *in-vitro* and *in-vivo* delays for bisoprolol are markedly different e.g., Formulation D (Example 3) shows an *in-vitro* delay of 2-4 hours (Table 1) yet results in an *in-vivo* delay of 8-14 hours (Table 5).

However, when bisoprolol is formulated in a pH-dependent system (Example 5), as presently claimed an *in-vitro* delay of 4-6 hours (Table 1) results in a matching *in-vivo* delay of 4-6 hours (Table 5). There is no way that one skilled in the art could predict from Noda et al. that employing a pH-independent polymer in conjunction with the formulation of the subject invention would lead to formulations showing different delays *in vivo* and *in vitro*, while employing

pH-dependent polymers, as presently claimed, would show comparable delays *in vitro* and *in vivo*.

The Handbook for Pharmaceutical Excipients fails to cure the deficiencies of Noda et al. First, there is no motivation in the references of record for combining the disclosures of Noda et al. and those in the Handbook for Pharmaceutical Excipients to obtain the claimed formulation. Moreover, even when combined, Noda et al. and the Handbook for Pharmaceutical Excipients fail to provide guidance to the artisan on how to prepare a formulation comprising at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer that exhibits a pH-dependent dissolution profile and that imparts a pH-dependent delay in bisoprolol release. Mere recitation of properties of polymers without more does not provide guidance to one of ordinary skill in the art on how to modify the formulations of Noda et al. to arrive at the presently claimed formulations. Accordingly, withdrawal of the 103 rejections based on Noda et al., alone, or in combination with the Handbook for Pharmaceutical Excipients is respectfully requested.

The Office rejects claims 7 and 8 under 35 U.S.C. § 103(a) as being unpatentable over Noda et al. in combination with Oshlack et al. (U.S. Patent No. 5,580,578). In response, Applicants submit that the combination of Noda et al. with Oshlack et al. does not render the claimed invention obvious.

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The deficiencies of Noda et al. are discussed above. Oshlack et al does not cure those deficiencies. The Official Action relies on Oshlack et al. for its purported disclosure of "the incorporation of a barrier layer between the medicinal core and the acrylic coating layer." Even assuming that Oshlack et al. does disclose such a barrier, this does not guide one of skill in the art to a pH-dependent polymer system as presently claimed.

Thus, the combination of Noda et al. with Oshlack et al does not teach or suggest the presently claimed invention and the 103 rejection based on the combination of Noda et al. and Oshlack et al. should be withdrawn.

In conclusion, Noda et al. taken alone or in combination with the secondary references fails to suggest, much less anticipate, the presently claimed invention. Accordingly, all the rejections based on Noda et al. should be withdrawn and such favorable action is respectfully requested.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 05-1323 (Docket No. 100338.54684US).

Respectfully submitted,

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